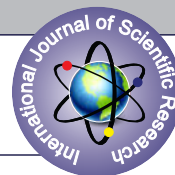


TO STUDY LEVELS OF FIBRINOGEN, D-DIMER AND IL-6 LEVELS IN PATIENTS OF COVID 19 AND THEIR CO-RELATION IN SEVERE VS MILD CASES OF COVID 19



Medicine

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ABSTRACT

Aim: To study levels of fibrinogen, D-dimer and IL-6 levels in patients of COVID 19 and their co-relation in severe vs mild cases of Covid 19.

Material and Method: The present retrospective cohort study was conducted in the department of Medicine at Chhatrapati Shivaji Subharti Hospital, Subharti Medical College, Meerut, UP. The study comprised of Covid positive patients during the July 2020 to January 2021. The severity of COVID-19 was defined according to WHO clinical management guidance of COVID-19. COVID-19 infection was confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR) assay from nose and throat swab samples.

Results: Mean fibrinogen, D-dimer and IL-6 level was found maximum among subjects with severe COVID category followed by moderate and mild category.

Conclusion: The pathogenic events manifest as deranged laboratory parameters, including fibrinogen, D-dimers, IL-6. Therefore, prophylaxis, early diagnosis, and prompt treatment remain the pillar of the management in COVID-19 patients and reducing mortality.

KEYWORDS

Fibrinogen, D-dimer, IL-6, COVID 19

INTRODUCTION:

A new infective outbreak, sustained by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and defined coronavirus disease 2019 (COVID-19), is now spreading all around the world. SARS-CoV-2 infection causes Coronavirus disease 2019 (COVID-19), and its severity ranges from asymptomatic to acute respiratory distress syndrome (ARDS), multiorgan failure, and eventually death¹. The overall rate of mortality due to COVID-19 has been estimated at 1% to 3%², whereas the reported mortality rate in hospitalized patients has varied from 6% to 34%^{3,4} and it can exceed 50% in patients in intensive care units (ICUs). Given these differences in disease severity and the potentially high in-hospital mortality, there is a need for early predictive biomarkers able to stratify patients according to their likelihood of a fatal outcome⁵.

Disseminated intravascular coagulation (DIC) is one of the major underlying causes of death in these patients. Consumption coagulopathy, which should be obviated in order to decrease mortality, arises in DIC with a decrease in fibrinogen and an increase in D-dimer levels. In fact, fibrinogen and one of its end products, D-dimer, have also been reported to have predictive value regarding the mortality of patients with non-Covid sepsis secondary to complications of DIC⁶. Fibrinogen, which is known as one of the acute phase proteins, is synthesized in high quantity by the liver in response to IL-1 and IL-6 derived stimulation, as well as is involved in fibrin formation as the last step of a triggered coagulation activity⁷.

Han et al⁸ revealed that the level of fibrinogen and its degradation products are not only higher in Covid-19 patients compared to healthy controls but also higher in critical Covid-19 patients compared to mild or moderate cases. On the other hand, fibrinogen is reported to be non-significant between surviving and non-surviving Covid-19 patients in a different cohort (5.16 vs. 4.51 g/L, p=0.149)⁹. However, studies on the predictive and prognostic values of coagulation parameters in the setting of patients with COVID-19 are still limited. The purpose of this retrospective study was to study the levels of fibrinogen, D-dimer and IL-6 levels in patients of COVID 19 and their co-relation in severe vs mild cases of Covid 19.

MATERIAL AND METHOD:

The present retrospective cohort study was conducted in the department of Medicine at Chhatrapati Shivaji Subharti Hospital, Subharti Medical College, Meerut, UP. The study comprised of Covid positive patients during the July 2020 to January 2021. During the study period, total 133 patients were recruited, but 9 failed to provide

the informed consent while 4 patients did not satisfy the inclusion criteria. The subjects were included and excluded according to the following mentioned criteria:

INCLUSION CRITERIA:

All Covid 19 positive patients.

EXCLUSION CRITERIA:

- Chronic liver disease
- Patients on anti-coagulant drugs
- Previous history of pulmonary embolism and DVT
- Patients who have not given written informed consent

The study was initiated after obtaining the approval from institutional ethics committee of the institution. Only after written informed consent was obtained from all potential participants then they were recruited.

COVID-19 was diagnosed on the basis of the WHO interim guidance. The severity of COVID-19 was defined according to WHO clinical management guidance of COVID-19¹⁰. Severe type was defined as followed: fever or suspected respiratory infection, plus one of respiratory rate > 30 breaths/min, severe respiratory distress, or SpO₂ < 90% on room air. A questionnaire was prepared to collect the patients demographic profile. After careful examination, patients were divided into mild, moderate and severe cases, according to guidelines laid down by Ministry of Health and family Welfare (MOHFW).

Mild cases:

- Patients with uncomplicated upper respiratory tract infection, may have mild symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache
- Without evidence of breathlessness or Hypoxia (normal saturation).

Moderate cases:

- Pneumonia with no signs of severe disease
- Clinical features of dyspnea and or hypoxia, fever, cough, including SpO₂

Severe cases:

- Clinical signs of Pneumonia plus one of the following; respiratory rate > 30 breaths/min, severe respiratory distress, SpO₂

COVID-19 infection was confirmed by real-time reverse transcription

polymerase chain reaction (RT-PCR) assay from nose and throat swab samples. Pneumonia was confirmed by computed tomography (CT) examination and coagulation test completed within 12 h after admission were enrolled. Coagulation tests, which fibrinogen (Fib) and D-dimer were performed using a Sysmex CS5100 automatic coagulation analyzer (Japan) and proprietary reagents.

STATISTICAL ANALYSIS:

Data was analysed using SPSS version 22.00 for windows; SPSS inc, Chicago, USA. Difference between two groups was determined using Anova test and the level of significance was set at $p < 0.05$. Logistic regression was used to associate factors with severity of COVID-19.

RESULTS:

Males were the dominant subjects in all the COVID categories. The mean age was 54.91 ± 13.92 , 57.73 ± 16.58 and 59.04 ± 20.01 years among subjects suffering from mild, moderate and severe COVID category respectively (table 1).

Table 1: Gender and age distribution among the study groups

COVID Category	Male		Female		Total
	N	%	N	%	
Mild	23	57.5	17	42.5	40
Moderate	27	67.5	13	32.5	40
Severe	30	75	10	25	40
Total	80	66.67	40	33.33	
Age (in years)					
	Mean		SD		
Mild	54.91		13.92		
Moderate	57.73		16.58		
Severe	59.04		20.01		

Mean fibrinogen and D-dimer was 4.13, 5.47, 6.31 g/L and 1.02, 1.41, 4.02 $\mu\text{g/ml}$ among subjects suffering from mild, moderate and severe COVID respectively. Mean IL-6 level was found maximum among subjects with severe COVID category followed by moderate and mild category. When mean fibrinogen, D-dimer and IL-6 level level was compared statistically between mild, moderate and severe COVID patients, it was found to be statistically significant as $p < 0.05$ (Table 2).

Table 2: Comparison of Fibrinogen, D-dimer and IL-6 level according to staging of COVID

COVID-19	Fibrinogen (g/L; normal range, 2-4)		D-dimer ($\mu\text{g/ml}$; normal range, 0-0.5)		IL-6 (pg/ml; normal range, <4.4)	
	Mean	SD	Mean	SD	Mean	SD
Mild	4.23	1.31	1.02	0.49	22.61	14.06
Moderate	5.47	1.47	1.41	0.68	53.48	40.92
Severe	6.31	1.89	4.02	1.36	278.52	110.32
Anova test	5.74		8.81		7.62	
p value	0.005*		<0.01*		0.002*	

*: statistically significant

According to logistic regression analysis, IL-6 (OR: 3.89, $P < 0.01$) was associated more with severity of COVID as compared to D-dimer (OR: 3.83, $P < 0.01$), fibrinogen (OR: 1.92, $P = 0.03$), though all the factors were significantly associated with severity of COVID (Table 3).

Table 3: Logistic regression of factors associated with severity of COVID-19

COVID-19	Multivariate analysis		
	OR	95%CI	p value
Fibrinogen (g/l)			
≤4	1 (Reference)	1.02-2.49	0.03*
>4	1.92		
D-dimer (μg/ml)			
<0.5	1 (Reference)	2.11-6.82	<0.01*
≥0.5	3.83		
IL-6 (pg/ml; normal range, <4.4)			
<0.5	1 (Reference)	2.47-7.80	<0.01*
>0.5	3.89		

*: statistically significant

DISCUSSION:

Coagulation dysfunction seems to be an important issue in patients

with COVID-19. It is generally believed that deterioration of coagulation parameters during the disease course is closely associated with COVID-19 worsening and death⁴.

As in previous studies^{2,11} cases were more often males. Besides, the male gender was found to be associated with severity. This fact would be in line with our observed effect of gender on severity.

In this study, mean fibrinogen and D-dimer level was comparatively and significantly higher among subjects suffering from severe COVID as compared to moderate and mild COVID category. According to logistic regression analysis, D-dimer was associated more with severity of COVID as compared to fibrinogen. Similar results were reported by Hai-Han Yu et al¹² and Hong-chun Luo et al¹³. Fei Zhou et al¹ too found that d-dimer greater than 1 $\mu\text{g/mL}$ on admission was associated with in-hospital death.

In our study, mean IL-6 level was found maximum among subjects with severe COVID category. According to logistic regression analysis, IL-6 was associated more with severity of COVID as compared to D-dimer and fibrinogen parameters. Similarly Aurora Jurado et al¹⁴ in their study revealed that on admission and at discharge, higher severity was significantly associated with higher levels of IL-6. Some of these hypotheses are apoptosis of T lymphocytes, an IL-induced pyroptosis-1 β , a direct cytopathic virus action on T lymphocyte, a bone marrow suppression due to cytokine storm (similar to that in sepsis) or pulmonary sequestration by bilateral pneumonia.

This study has several limitations. First, our study might have selection bias because it was a single-center along with its retrospective design. Second, due to difference of patient's size and medical resources, the lengths from illness onset to admission of the included patients might not be representative, which might influence D-dimer and fibrinogen levels on admission.

CONCLUSION:

The COVID-19 pandemic has put medical knowledge to the challenge of finding treatment for a pathogen whose behavior is yet to be defined. The pathogenic events manifest as deranged laboratory parameters, including fibrinogen, D-dimers, IL-6. Therefore, prophylaxis, early diagnosis, and prompt treatment remain the pillar of the management in COVID-19 patients and reducing mortality.

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